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A metapopulation model for the spread and persistence of contagious bovine pleuropneumonia (CBPP) in African sedentary mixed crop-livestock systems

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Abstract (226 words)

Contagious bovine pleuro-pneumonia (CBPP) is endemic in several developing countries. Our objective is to evaluate the regional CBPP spread and persistence in a mixed crop-livestock system in Africa. A stochastic compartmental model in metapopulation is used, in which between-herd animal movements and the within-herd infection dynamics are explicitly represented. Hundred herds of varying size are modelled, each sending animals to *n* other herds (network degree). Animals are susceptible, latent, infectious, chronic carrier or resistant. The role of chronic carriers in CBPP spread being still debated, several chronic periods and infectiousness are tested. A sensitivity analysis is performed to evaluate the influence on model outputs of these parameters and of pathogen virulence, between-herd movement rate, network degree, and calves recruitment. Model outputs are the probability that individual- and group-level reproductive numbers R_0 and R_* are above one, the metapopulation infection duration, the probability of CBPP endemicity (when CBPP persists over five years), and the epidemic size in infected herds and infected animals. The most influential parameters are related to chronic carriers (infectiousness and chronic period), pathogen virulence, and recruitment rate. When assuming no CBPP re-introduction in the region, endemicity is only probable if chronic carriers are assumed infectious for at least one year and to shed the pathogen in not too low an amount. It becomes highly probable when assuming high pathogen virulence and high recruitment rate.

Keywords: Epidemic model; Network; Sensitivity Analysis; Disease Endemicity; Chronic Carrier

1. Introduction

Contagious bovine pleuropneumonia (CBPP) is a respiratory disease of cattle caused by *Mycoplasma mycoides* subsp. *mycoides* small colony (*MmmSC*) (Cottey and Yeats, 1978; Nicholas and Bashidurin, 1995). A former 'list-A' disease of World Organisation for Animal Health (OIE) (Lefèvre, 2000; OIE, 2003), CBPP is a major concern for numerous developing countries (because of livestock mortality and production losses and disease control costs). For example, the Pan African programme for the Control of Epizooties (PACE) (this programme was implemented by the African Union Interafrican Bureau for Animal Resources [AU-IBAR] in 32 African countries and was principally funded by the European Commission with the support of the participating African countries) has identified CBPP as the second most important transboundary disease in Africa after rinderpest (Tambi et al., 2006).

Contagion occurs through direct and repeated contacts between infected and susceptible cattle, essentially through expectorations of coughing animals (Nicholas and Bashidurin, 1995; Provost et al., 1987). Cattle movements (social or contractual loaning, purchases and sales of animals in local markets) are the main risk of between-herd CBPP spread in that farming system (Bonnet et al., 2005; Laval and Workalemahu, 2002; Lesnoff et al., 2002a). CBPP shows a large range of severity and signs (Provost et al., 1987). Some animals appear to be naturally resistant. Subclinical forms are frequent. Severe respiratory signs are the most–prominent features observed in the clinical cases, and are associated with typical lesions of pleurisy and pneumonia. Recovered cattle often have necrotic lung tissue, encapsulated in sequestra where mycoplasmas can survive. The involvement of chronic carriers in the perpetuation of the infection has been suggested by several authors (Egwu et al., 1996; Mahoney, 1954; Martel et al.,

1985; Provost et al., 1987). It is still debated since carriers' infectivity has not been demonstrated yet. For example, Windsor and Masiga (1977) did not observe CBPP transmission after challenging experimentally susceptible animals with chronic carriers. CBPP outbreaks have essentially been described at the herd level, in experimental (Hudson and Turner, 1963; Thiaucourt et al., 2000; Yaya et al., 1999) or natural conditions (Bygrave et al., 1968; Lesnoff et al., 2004b). Nevertheless, the threat in African countries goes beyond the individual farms and need to be evaluated at a higher level (an infected herd is a risk for neighbouring herds due to frequent and uncontrolled animal movements). CBPP outbreaks in a farmers community, in a village or in a region are unfortunately much more complex to quantify and poorly documented (at the knowledge of the authors, no incidence data are available).

For better understanding the CBPP persistence in a region and being able to evaluate the impact of different control strategies at this level (e.g. vaccinations or treatments and isolation of seek animals), it is necessary to develop dynamics models. A CBPP spread metapopulation model was already developed for representing three connected large-size ($\geq$ 50 to more than 3,000 animals) mobile herds of a pastoral community in East Africa (Mariner et al., 2006). We propose a metapopulation model for a sedentary mixed crop-livestock system, composed of a larger number of herds, sedentary and of small size.

Within a small herd, it has been shown that CBPP cannot persist if infected animals are not re-introduced or if chronic carriers are not involved in the transmission dynamics (Lesnoff et al., 2004a). However, spatial heterogeneity due to the structure of the population (here the farming system structured into herds) influences disease persistence and dynamics (Ball et al. 1997). Asynchrony in disease dynamics may arise

among herds within a region, allowing a global persistence of a disease because of a 'rescue effect': moving infected animals may reintroduce the disease in herds where it has locally died out (Grenfell and Harwood, 1997; Lloyd and May, 1996). In such a context, the disease may persist in the metapopulation of herds (or the infection duration of the metapopulation may be longer than in a single herd) without the need of disease re-introductions or without assuming any role played by CBPP chronic carriers in the disease spread.

In the present paper, a stochastic compartmental model is developed for studying the spread and persistence of CBPP in a newly infected area, representing a hypothetic metapopulation of sedentary herds in a mixed-crop livestock farming system. No CBPP re-introduction or control interventions are assumed in the area (such as vaccination, animal isolation and slaughtering, or chemotherapy). The objective is to identify the most influential parameters on the invasion threshold at the metapopulation level, on the infection duration and the probability of CBPP endemicity (disease persistence over more than 5 years) in a bovine metapopulation, and on the epidemic size at the herd and at the individual levels. To fulfil this objective, we analyse the sensitivity of these model outputs to variations in model parameters, and especially parameters generally influencing disease spread and persistence (level of recruitment, pathogen virulence, between-herd animal movement, and network degree) and parameters with uncertain values (shedding period and infectiousness of chronic carriers).

2. Model framework

The model is compartmental, stochastic and uses discrete time with a time interval of one week. The metapopulation consists in a set of herds exchanging animals. The model

explicitly represents the within-herd CBPP dynamics and the between-herd animal movements. A simulation consists in several repetitions of CBPP spread in the metapopulation over a defined time interval.

2.1 Within-herd spread of CBPP

The within-herd model is adapted from different models developed in a research project in the Ethiopian highlands (Balenghien et al., 2004; Lesnoff et al., 2002b, 2004a and 2004c) and is briefly described thereafter (Fig. 1).

The model represents managed open herds of cattle with entries in and exits from the herds. All the within-herd model parameters are described in Tab. 1. Young animals (< 6 months) are not represented because they are more resistant to CBPP than adults are. They are assumed not contributing to the spread of the disease (Curasson, 1942; Provost et al., 1987). The natural recruitment rate among animals born in the herd corresponds to the birth rate times the probability of still being in the herd six months after birth. A proportion p_{res} of recruited animals are naturally resistant to infection, other being susceptible. In addition, animals not born in the herd may also enter the herd (e.g. by purchases, gifts or contractual loans). Exits correspond to deaths and living animals that leave the herd (sales, slaughtering or contractual loans).

In herd x, animals can be of five infection states: susceptible (S_x), incubating (infected but not yet infectious) (E_x), infectious (I_x), chronically infected (not or slightly infectious; Q_x), and recovered (immunised) or naturally resistant to infection (not infectious; R_x). Consistent durations in states E, I, and Q are assumed (Tab. 1). CBPP transmission between animals is density-dependent. Infectious individuals have a disease-related mortality, which largely increases with pathogen virulence (Tab. 1).

Transitions between infection-states, deaths and movements due to the sell-and-purchase process are simulated from multinomial random generators that allow taking into account of possible disease fade-outs, characteristics of small populations (Anderson and May, 1991) (Tab. 2).

2.2 Between-herd spread of CBPP

A metapopulation of N cattle herds representing a typical sedentary mixed crop-livestock area is modelled. Herds are of various sizes, ranging from 1 to 40 animals with 8 animals on average. This represents the observed heterogeneity among this kind of system (e.g. Bonnet et al., 2005; Lesnoff et al., 2002a). Each herd is connected to exactly n other herds (corresponding to the network degree) in which it can eventually send animals. For each realisation of the model, n herds are randomly chosen for each herd among the N-1 possible herds before the initial introduction of the disease in the area.

Among animals leaving herd x (on average πZ_x animals for a movement rate from the herd π and infection-state Z, where Z_x is the number of animals of state Z in herd x), a proportion p_{in} stays in the modelled area, i.e. move from herd x to one of the n herds connected to x. This proportion has been adjusted to ensure the demographic equilibrium of the metapopulation (i.e. on average the metapopulation size is consistent over time). The destination of each movement is randomly chosen among the n herds with a uniform probability. Hence, each of these n herds has a chance $1/n$ to be chosen for each movement. Any other probability distribution could be used if information was available about preferences that may exist towards a given herd among all potential

source herds. Assuming a uniform probability for this choice, the average number of animals of state Z entering herd x is:

$$\Omega(Z_x) = \sum_{i=1}^{i=T} p_{in}\,\pi\,Z_i \frac{\sigma_{ix}}{\sum_{j=1}^{j=T}\sigma_{ij}} = \sum_{i=1}^{i=T} p_{in}\,\pi\,Z_i \frac{\sigma_{ix}}{n},$$

with $\sigma_{ij} = 1$ if herd j is part of the n herds of destination of herd i, 0 otherwise (see Tab. 1 for a definition of other parameters). Animals entering herd x (purchases, loans, etc.) can be of any infection-state (*S, E, I, Q, R*). No neighbouring relationships, as for example contacts at pasture, is modelled (animals movements are considered as the only cause of between-herd infection).

2.3 Scenarios

Scenarios are defined based on different levels of chronic carriers infectiousness β_Q and shedding period duration d_Q, of pathogen virulence (varying both the transmission rate β_I and the disease-related mortality of infectious animals α in status *I*), of within-herd calves recruitment rate, of the network degree of the metapopulation, and of between-herd animal movements.

The infectiousness and the shedding period of chronic carriers are debated and the corresponding parameters values remain fully uncertain. Four levels of β_Q (all far lower than infectiousness of animals in state *I*; Tab. 3) and two values of d_Q (26 and 52 weeks) are tested. Moreover, in the literature, variable levels of virulence (in terms of incidence and disease-related mortality) have been reported (Masiga et al., 1996; Provost et al., 1987). In the article, two levels of pathogen virulence are tested: low-virulence (*LVIR*) vs. high-virulence (*HVIR*) (Tab. 3).

Although they are known to influence the spread of pathogens in structured populations (Keeling and Eames, 2005; Kiss et al., 2006; Vincente et al., 2007), the recruitment rate, the between-herd contact structure, and the associated animal movement rate depend on the situation and on the farming system. Three recruitment rates, three network degrees (represented by the number of herds to which a herd is connected and to which it can send animals; the highest degree corresponds to a complete network, all herds being in contact with each other) and two movement rates are tested (Tab. 3).

A full factorial design is built by combining all the levels of the six variation factors, resulting in 288 scenarios. For each scenario, 200 realisations are performed over a 10-year simulation period. The number of realisations is a compromise between steady output distributions and simulation time. Five incubating animals are initially introduced in randomly chosen herds of the metapopulation. The metapopulation consists in $N = 100$ herds. No re-introduction of the disease is allowed.

2.4 Output

Three indicators of the disease spread and persistence are evaluated.

First, the proportions of model realisations with a simulated animal-level (R_0) and group-level (R_*; *Ball* et al. 1997) reproductive numbers above one are evaluated (denoted thereafter by $P(R_0>1)$ and $P(R_*>1)$ respectively; Tab. 4). The more extensively used basic reproductive number (R_0) has been extended in multiple ways to account for example for depletion in susceptible individuals (Keeling and Grenfell, 2000) or for population structure (Keeling, 1999; Fulford et al., 2002). However, R_0, which is an individual-based criteria, is less appropriate to predict disease invasion in a metapopulation framework than the group-level reproductive number R_*, as

206 demonstrated using a phenomenological mixing model (Ball et al., 1997; Ball, 1999;
207 Ball and Lyne, 2001; Ball and Neal, 2002) or a mechanistic mixing model (Cross et al.
208 2005, 2007). In the present article, R_0 and R_* are simulated for each realisation of the
209 model. Initially, a single animal in state *E* (index case) is introduced in a randomly
210 chosen herd (index herd). The herds forming the metapopulation have a uniform
211 probability of being chosen and this choice is made independently for each model
212 realisation. All other animals in the metapopulation are initially either susceptible
213 (proportion 1-p_{res}) or naturally resistant (proportion p_{res}). On the one hand, R_0 is
214 calculated as the number of newly infected animals (leaving state *S* because of
215 infection) in the metapopulation caused by the index case over its lifetime, this
216 individual being allowed to move between herds. Newly infected animals can infect
217 animals as soon as infectious, resulting in a local depletion in susceptible animals
218 available for infection by the index case. On the other hand, R_* is calculated as the
219 number of newly infected herds in the metapopulation due to movements of infected
220 individuals from the index herd over its infection duration (Cross et al., 2005). Animals
221 in newly infected herds can infect animals as soon as infectious. This results in
222 decreasing the number of susceptible animals available for infected animals from the
223 index herd. As simulated with the model, these estimates of R_0 and R_* account for the
224 population structure, animal movements, and the depletion in susceptible animals, and
225 thus differ from traditional analytical values, which assume an infinite susceptible
226 population.
227 Second, the infection duration of the metapopulation is evaluated for each model
228 realisation, and denoted thereafter by *InfDur* (Tab. 4). When chronic carriers are
229 assumed not infectious, the metapopulation is considered to be infected as long as at

230 least one animal in state *E* or *I* is still present. When chronic carriers are assumed
231 infectious, the metapopulation is considered to be infected as long as at least one animal
232 in state *E*, *I*, or *Q* is still present. The average duration and the associated standard error
233 are calculated. Moreover, we define CBPP to be endemic when it persists over more
234 than five years. Hence, the probability of endemicity (denoted by *P(endemic),* Tab. 4) is
235 calculated as the proportion of realisations in which the infection duration is above five
236 years.
237 Third, the epidemic sizes at both the individual and the herd levels are evaluated, i.e. the
238 cumulative incidence in infected individuals (herds, respectively) over the simulation
239 period. The epidemic size at the individual level is the cumulative number of animals
240 newly in state *E* in the metapopulation. A herd is considered to have been infected over
241 the simulation period if an animal in state *E* or *I* (or also in state *Q* in scenarios
242 assuming chronic carriers to be infectious) had belonged at least for one time interval to
243 the herd. Epidemic sizes are denoted thereafter by *EpSiz(I) and EpSiz(H)* and for the
244 individual and the herd levels respectively (Tab. 4).
245

246 **3. Sensitivity analysis**

247 Based on the model realisations implemented in the full factorial design, the
248 contributions of the variation factors to the outputs variability are evaluated using a
249 linear regression approach (Saltelli et al., 2000). For each output, a linear regression
250 model is fitted with all the principal effects of the factors and their first-order
251 interactions. A minimum variance criterion is defined: factors or interactions accounting
252 for more than 1% of variance are retained in the model. The global contribution of

253 factor *i* (including the principal effect plus interactions in which factor *i* is involved) to
254 the variation in output *y* is:

255 $$C_i^y = \frac{SS_i^y + \frac{1}{2}\sum_j SS_{i:j}^y}{SS_{tot}^y},$$

256 with SS_{tot}^y the total sum of squares of the model for output *y*, SS_i^y the sum of squares
257 related to the principal effect for factor *i* for output *y* (nil if factor *i* is not retained in the
258 model), $SS_{i:j}^y$ the sum of squares related to the interaction between factor *i* and factor *j*
259 for output *y* (nil if this interaction is not retained in the model). The sum of the
260 contributions for output *y* equals the coefficient of determination of the regression
261 model R^2. In the article, the sensitivity of the outputs is then analysed only in relation to
262 factors contributing the most to their variations.
263
264 **4. Results**
265 **4.1 Factors contributing to variation in model output**
266 The factors contributing the most to the model output variations are the parameters
267 related to chronic carrier animals (β_Q and d_Q), the pathogen virulence, and the
268 recruitment rate (Fig. 2). The movement rate and the network degree only contribute to
269 the variation in *P(R*>1)*.
270 Depending on the outputs, the most contributing parameters explain all together from
271 52% to 95% of the variance. β_Q and d_Q are highly influential, explaining together from
272 26 to 66% of the output variance. Pathogen virulence explains from 10 to 18% of the
273 output variance, except for *P(R0>1)* for which it is with β_Q the most influent parameter.

Calves recruitment explains from 0 to 15% of the output variance, contributing essentially to the variation in *P(endemic)*, *EpSiz(I)* and *EpSiz(H)*.

4.2 Reproductive numbers at the metapopulation level

R_0 shows different patterns depending on LVIR or HVIR scenarios. In LVIR, the average R_0 and *P(R0>1)* are always below 1 and 30% respectively, *P(R0>1)* only slightly increasing with β_Q and d_Q (Fig. 3). In HVIR, however, the average R_0 is above one, even when $\beta_Q = 0$. $P(R_0>1)$ ranges from 24 to 65% (Fig. 3) with a net influence of chronic parameters (although levels $\beta_Q = 0$ and $\beta_Q = \beta_I/1000$ show similar results).

In contrast, R^* shows low values for both LVIR and HVIR. In all scenarios, the average R^* and *P(R*>1)* are below one and 20% respectively. This shows that under the tested range of parameters' values it is difficult for the disease to invade the metapopulation.

In LVIR, *P(R*>1)* is even below 5% and always nil when $\beta_Q = 0$ (Fig. 4a). In HVIR, *P(R*>1)* clearly increases with β_Q, d_Q, and the movement rate (Fig. 4b).

As indicated in Fig. 2, the network degree also contributes to *P(R*>1)*. *P(R*>1)* is positively correlated to this parameter, but only when $\beta_Q = \beta_I/100$ or $\beta_Q = \beta_I/50$ (patterns are not clear for lower chronic infectiousness).

4.3 Duration of the metapopulation infection and probability of endemicity

β_Q, d_Q, pathogen virulence, and recruitment rate are the parameters influencing the most *InfDur*. In all scenarios, average *InfDur* is shorter than 6 months when chronic carriers are assumed not infectious (Fig. 5). The longest average *InfDur* in LVIR and HVIR are above 4 and 8 years, observed with $\beta_Q = \beta_I/50$, $d_Q = 52$ weeks and a high recruitment rate. By model construction, *InfDur* increases with d_Q when $\beta_Q > 0$ (Fig. 5).

298 Nevertheless, whereas d_Q is doubled (26 to 52 weeks), average *InfDur* is tripled for
299 $\beta_Q = \beta_I/50$ and a high recruitment rate. The recruitment rate increases average *InfDur*
300 but essentially when $\beta_Q = \beta_I/100$ or $\beta_I/50$ and $d_Q = 52$ weeks.
301 Concerning CBPP endemicity, *P(endemic)* is nil when $d_Q = 26$ weeks, and when
302 $d_Q = 52$ weeks and $\beta_Q = 0$ or $\beta_I/1000$. In other situations, *P(endemic)* is highly sensitive
303 to β_Q, pathogen virulence, and recruitment rate (Fig. 6). Endemicity becomes highly
304 probable (*P(endemic)* > 0.50) when assuming a high recruitment rate in HVIR.
305
306 **4.4 Epidemic size in infected herds and in infected individuals**
307 When $d_Q = 26$ weeks, average *EpSiz(H)* only varied from 5 to 8% of the herds
308 depending on the other variation factors considered (Fig. 7). The infected herds
309 correspond mostly to the initially infected herds (five infected animals are introduced
310 initially in randomly chosen herds in a metapopulation of 100 herds). When $d_Q = 52$
311 weeks, average *EpSiz(H)* shows a higher variability and increases with β_Q, the pathogen
312 virulence, and the recruitment rate (Fig. 7). Nevertheless, average *EpSiz(H)* remains
313 lower than 15% in all LVIR scenarios, and in HVIR overpasses 20% only for
314 $\beta_Q = \beta_I/100$ or $\beta_I/50$ with a high recruitment rate.
315 The same kind of results are found for average *EpSiz(I)*, but with a higher sensitivity to
316 variation factors (even when $d_Q = 26$ weeks) (Fig. 8) since *EpSiz(I)* results from within-
317 herd infection that can spread at least in the initially infected herds.
318 For both *EpSiz(H)* and *EpSiz(I)*, the model shows few differences between scenarios
319 assuming no vs. a low infectiousness of the chronic carriers (Fig. 7 and 8).
320
321 **5. Discussion**

Endemicity of CBPP is assumed in several regions of Africa, among which regions with mixed crop-livestock systems (FAO, 2003). The proposed model has been developed to represent the spread of CBPP between cattle herds in a mixed crop-livestock farming system and to evaluate if the disease could be endemic in a (originally CBPP free and naïve) metapopulation of herds assuming no disease re-introduction. In our simulations and based on the scenarios considered, infectiousness and shedding period duration of chronic carriers, pathogen virulence, and calving recruitment rate are the most influential factors on the probability for CBPP to invade the metapopulation, the CBPP endemicity and the infection sizes. In contrast, although diseases are known to generally better persist in heterogeneous populations (Lloyd and May, 1996), the between-herd movement rate and the network degree linking the herds do not influence significantly the model outputs, except $P(R_* > 1)$. One important result is that CBPP endemicity as defined in our model (and assuming no disease re-introduction) is only probable if chronic carriers are assumed infectious for a long period of time (one year in the article) and to shed the pathogen in not too low an amount. It becomes highly probable when assuming and a high pathogen virulence and a high level of recruitment. This demonstrates that chronic carriers, if infectious, are a possible determinant of CBPP persistence in African sedentary farming systems. Nevertheless, the ability of chronics carriers to transmit the disease has still never been proved (Windsor and Masiga, 1977). Recent experimental studies (Huebschle et al., 2006a,b) showed that CBPP seek animals treated with antibiotics and surviving to the disease (similarly to naturally chronics carriers) can remain infectious. However, infectiousness is mitigated compared to untreated and seek animals. Another obvious possible determinant of CBPP persistence is the regular re-introduction of seek animals from other endemic regions,

346 reproducing a source-sink process. More biological researches on the evaluation of the
347 infectiousness of chronic carriers are needed for prioritising one of these two
348 hypotheses.
349
350 The probability for a disease to invade a metapopulation has been shown to be better
351 understood at the patch-level than at the individual-level (Ball and Neal, 2002). A
352 group-level reproductive number has been introduced as an indicator of the capability of
353 a pathogen to invade a human population partitioned in many small households (Ball et
354 al., 1997; Ball, 1999; Ball and Lyne, 2001; Ball and Neal, 2002). It has been extended
355 to the case of a structured population with explicit movements of individuals
356 (mechanistic metapopulation model) and compared to R_0 (Cross et al., 2005, 2007).
357 Our results are coherent with expectations: the probability of having newly infected
358 individuals is mainly influenced by the transmission rates (i.e. what happens at a local
359 scale), whereas the probability of having new herds infected is also influenced by the
360 movement rate and the network degree (Cross et al., 2007). However, the movement
361 rate and the network degree do not influence other model outputs. Here, the network
362 degree should be highly related to the herd epidemic size, as the highest number of
363 herds that can be infected per infected herd equals the network degree. However, CBPP
364 spreads very slowly in the metapopulation and each herd contributes to a very low
365 number of newly infected herds (average $R_* < 1$, whatever the network degree). As a
366 result, the network degree – even if low – does not constrain the spread of the disease
367 here and we do not observe a maximum in CBPP persistence for intermediate level of
368 coupling (Keeling and Eames, 2005). As pointed out by Cross et al. (2005), chronic
369 diseases, with a longer infectious period and thus more between-herd movements of

370 infected animals over the infectious period, may perceive a structured population as an
371 homogeneous one. In contrast, when assuming chronic carriers not to be infectious, the
372 population structure has a strong impact on CBPP spread and persistence, the movement
373 rate being too low to enable CBPP endemicity (Jesse et al., submitted).
374
375 The proposed stochastic model includes a compartmental model of the within-herd
376 spread of CBPP, adapted from models developed in a research project in the Ethiopian
377 highlands (Balenghien et al., 2004; Lesnoff et al., 2002b, 2004a and 2004c). A
378 metapopulation approach has been used to extend the within-herd model to a regional
379 infection dynamics. The modelled region is a population of herds of different sizes. The
380 within-herd infection dynamics is explicitly represented, as well as animal movements
381 between herds, known as a main source of CBPP regional spread in sedentary mixed
382 crop-livestock systems (Bonnet et al., 2005; Laval and Workalemahu, 2002; Lesnoff et
383 al., 2002a). All the model parameters have a biological meaning and can be estimated
384 from field data or experiment (basically from within-herd incidences and animal
385 exchange rates). For example, the present model has been calibrated using longitudinal
386 data on naturally and newly CBPP-infected herds obtained from a follow-up survey
387 formerly implemented in Ethiopia in small and sedentary herds of mixed crop-livestock
388 systems (Lesnoff et al., 2002a, 2004b).
389
390 In the literature, three general approaches have been used to model the regional spread
391 of a pathogen in a metapopulation of herds. In the first approach, both the
392 metapopulation structure and the variability in the within-herd disease spread are
393 modelled (Ball et al. 1997; Cross et al. 2005; Hess, 1994, 1996; Swinton et al., 1998;

394 Vazquez, 2007), as proposed in the present model. A second approach accounts for the
395 metapopulation structure but without representing the within-herd spread of the disease.
396 This approach has been frequently used to model the spread of highly contagious
397 diseases (e.g. for applications to classical swine fever: Mangen et al., 2002; to foot-and-
398 mouth disease: Le Menach et al., 2005; to avian influenza: Le Menach et al., 2006),
399 because the within-herd prevalence quickly reaches equilibrium for such diseases. For
400 example in foot-and-mouth disease, 90% of the animals in a herd become infected in
401 less than a week on average after a primary infection occurs (Le Menach et al., 2005),
402 i.e. in each infected herd prevalence predictably and rapidly rises to 90%. This second
403 approach has also been used to model disease spread in wildlife metapopulation (Hess,
404 1996; Gog et al., 2002; McCallum et al., 2002), and more recently to model the spread
405 of *Salmonella* between cattle herds (Xiao et al., 2007). A third approach assumes the
406 region as a unique population. In this approach, the evolution in individual infection
407 statuses (e.g. SEIR) is modelled without representing the structure of the host
408 metapopulation (e.g. in a vector-borne disease: Tran and Raffy, 2006; in an air-borne
409 disease for the animal reservoir: Iwami et al., 2007).
410 Although the last two approaches are far simpler than the first one, they are inadequate
411 when modelling the spread of CBPP in mixed crop-livestock systems in Africa. On the
412 one hand, the within-herd CBPP spread is too slow to be neglected as it is done in other
413 diseases. The within-herd CBPP prevalence (and therefore the contribution of herds to
414 the outbreak) vary over time and among infected herds and the epidemiological
415 structure does not reach quickly a consistent equilibrium, which is needed to neglect the
416 within-herd disease spread in the metapopulation model. On the other hand, an average
417 transmission rate for a homogeneous region cannot be estimated because of – as far as

418 we know – a lack of animal-level incidence data at the regional scale in mixed crop-
419 livestock systems in Africa. The within-herd transmission rate cannot be used because
420 the regional transmission rate is expected to be far lower than this local transmission
421 rate. Moreover, an average regional model assumes a homogeneous mixing between
422 animals in the region, whereas animals are structured into herds in the field. A model of
423 CBPP spread in a pastoral area has been proposed in which three very large herds were
424 considered (Mariner et al.,2006). In this model, both the within- and the between-herd
425 CBPP spread were represented. The between-herd spread was modelled using a
426 between-herd transmission rate, resulting in a need to estimate this global transmission
427 rate. In contrast, in the proposed model CBPP infection dynamics are modelled at the
428 within-herd scale (for which data are available to estimate the infection parameters) and
429 the between-herd spread is mechanistically modelled, in relation with animal
430 movements which are explicitly modelled and which can be quantified in the field. This
431 is an original approach to model the between-herd spread of CBPP.
432
433 The representation of between-population individual movements is of particular interest
434 in studying the epidemiology of long-lasting diseases. In human epidemiology,
435 individual movements are generally "go-and-return" like. Most of the movements are
436 then visits of short duration compared to the infection duration. In that context,
437 modelling explicit movements (mechanistic approach) or using a phenomenological
438 formulation was found to be almost equivalent (Keeling and Rohani, 2002). In animal
439 epidemiology, however, individual movements are generally of the type "go-without-
440 return" (sales or purchases) or long lasting visits (loans that can last for several months).
441 Hence, the mechanistic approach used in our model seems here more appropriate.

The heterogeneity in herd sizes induces variations in the within-herd spread of CBPP among infected herds and therefore in the risk of between-herd infection and in the global dynamics. Representing this heterogeneity, as for example in our mechanistic metapopulation model, is an interesting extension of previous disease dynamics models. Nevertheless, one main difficulty is to model the contact rate and the within-herd transmission rate. In the present model, we assume that herds are small enough (herd sizes range from 1 to 40 animals as observed in the field; Bonnet et al., 2005; Lesnoff et al., 2002a) to consider that the contact rate between animals increases linearly with herd size and that the within-herd force of infection is density-dependent (McCallum et al., 2001). In systems with larger herds, however, the contact rate may reach a saturation threshold and the density-dependent assumption for the within-herd force of infection may not be adequate. For example, cattle herds in pastoral areas may be so large that the number of contacts between animals is constant whatever the herd size, the probability of contact with an infectious animals being thus frequency-dependent (McCallum et al., 2001). If the assumption about the force of infection changes, the within-herd transmission rate should be re-estimated per herd size class or to be an explicit function of the herd size. Such questions were not under the scope of the present article and were not explored but are interesting perspectives.

In mixed crop-livestock systems, relationships between neighbouring herds other than animal movements are not the main factor of between-herd spread (Bonnet et al., 2005; Laval and Workalemahu, 2002; Lesnoff et al., 2002a). Here, animal movements are not related to the distance between herds since the modelled area is small. In that situation,

466 random exchanges are realistic. Qualitative observations on the field indicate that – on
467 the modelled scale – a farmer can exchange animals with a farm located at either 100m
468 or 5km from his farm with the same probability, exchanges being at this scale more
469 related to local opportunities and social relationships. If a larger region was to be
470 modelled, then the distance between herds may influence animal exchanges. Moreover,
471 for the model to be general and to take into account all known risk factors such as
472 animal divagation, neighbouring relationships should be further added to the model.
473 Research is needed to account for space in the modelled network.
474
475 Finally, the proposed model is sufficiently generic to be adapted to other directly
476 transmitted diseases with a SEIR infection dynamics and for which the main risk factor
477 of regional spread is individual movements. The only constraint is to estimate the model
478 parameters: the within-herd force of infection, the range of herd sizes for which this
479 force of infection applies and the movement rates. From a practical point of view, our
480 model can help in the future in identifying control measures for preventing or reducing
481 the herd- and animal-level CBPP prevalence in a region (such as vaccinations,
482 chemotherapy or isolation of seek animals). By studying the associated farmer losses,
483 such a modelling approach can help in increasing the economic efficiency of control
484 measures.
485

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658

658 Table 1

659 Parameters of the metapopulation model for the spread of contagious bovine

660 pleuropneumonia (CBPP) in case of low virulence pathogen (LVIR)

Parameter	Definition	Value[a]
d_E	Duration (in weeks) of the incubation period (state *E*)	6
d_I	Duration (in weeks) of the infectious period (state *I*)	4
d_Q	Duration (in weeks) of the chronic period (state *Q*)	52
α	Disease-related mortality rate	0.036
β_I	Transmission rate by infectious individuals	0.06
β_Q	Transmission rate by chronic carriers	0
p_{res}	Proportion of naturally resistant individuals	0.10
Q	Proportion of individuals becoming infectious after the incubation period (from state *E* to state *I*)	0.39
b	Recruitment rate	0.0028
μ	Natural mortality rate	0.0012
π	Movement rate from each herd	0.0033
p_{in}	Proportion of the movements occurring within the modelled zone, i.e. between two modelled herds	0.40
N_x	Size of herd *x*	1-40 (mean 8)
T	Number of interacting herds	100
n	Number of herds in which one herd can send animals (i.e. network degree)	10

661 [a] Parameters of the within-herd dynamics are adjusted to provide the same results as in Lesnoff et al.

662 (2005; Tab. 1). On average in LVIR, the total number of newly infected animals (state *E*) from the disease

663 introduction to the disease extinction represents 35% of the herd, 39% of which become infectious (state

664 *I*), and 14% of the infectious animals die from CBPP. Values of μ and π correspond to an annual

665 mortality of 5% and an annual movement rate from each herd of 15%.

666

666 Table 2

667 Definition of the stochastic model for the within-herd spread of CBPP in herd *x*

Event	Health-state transition	Probability[a]
Infection	$S_x \rightarrow E_x^1$	$Bin\left(S_x, 1-\exp\left[-\beta_I \sum_{k=1}^{k=d_I} I_x^k\right]\right)$
End of the latent phase	$E_x^{d_E} \rightarrow I_x^1, Q_x^1$	$Mul\left(E_x^{d_E}, q\right)$
End of the infectious phase	$I_x^{d_I} \rightarrow Q_x^1$	1
End of the chronic phase	$Q_x^{d_Q} \rightarrow R_x$	1
Disease-related mortality	$I_x^k \rightarrow out$	$Bin\left(I_x^k, \alpha\right)$
Birth	$in \rightarrow S_x, R_x$	$Mul\left(Bin\left(N_x, b\right), p_{res}\right)$
Natural mortality and movement from the herd	$Z_x \rightarrow out$	$Bin\left(Z_x, \mu+\pi\right)$

668 [a] *Bin* denotes for binomial distribution, *Mul* for multinomial distribution.

669

669 Table 3

670 Range of values for parameters of the metapopulation model for the spread of
671 contagious bovine pleuropneumonia (CBPP) used to defined the scenarios and the
672 factorial experiment in the sensitivity analysis (in bold, values of the reference scenario
673 used in Tab. 1)

Parameter	Definition	Range of values
$[\alpha, \beta_I]$	Pathogen virulence[a] defined by two parameters: [disease-related mortality , transmission rate by infectious animals]	**LVIR: [0.036 , 0.06]**, HVIR: [0.300 , 0.50]
d_Q	Chronic period duration (in weeks)	26, **52**
β_Q	Transmission rate by chronic carriers	**0**, β_I /1000, β_I /100, β_I /50
b	Recruitment rate	0.0014, **0.0028**, 0.0056
$p_{in}\pi$	Between-herd movement rate	**0.0013**, 0.0026
n	Network degree	2, **10**, 99

674 [a] LVIR: low virulence scenario; HVIR: high virulence scenario. On average in *LVIR*, the total number of
675 newly infected animals (state *E*) from the disease introduction to the disease extinction represents 35% of
676 the herd, 39% of which become infectious (state *I*), and 14% of the infectious animals die from CBPP. In
677 *HVIR*, the correspondent proportions are 80, 39 and 70%.

678

678 Table 4

679 Definition of the outputs of the metapopulation model for the spread of contagious

680 bovine pleuropneumonia (CBPP)

Output	Definition
R_0	Individual-level reproductive number
R_*	Group-level reproductive number
$P(R_0>1)$	Probability to have R_0 above one
$P(R^*>1)$	Probability to have R^* above one
InfDur	Duration of the metapopulation infection
P(endemic)	Probability of CBPP endemicity (*InfDur* > 5 years)
EpSiz(H)	Epidemic size in infected herds (cumulative incidence in infected herds over the simulation period)
EpSiz(I)	Epidemics size in infected individuals (cumulative incidence in animals in state *E* over the simulation period)

681

682

682 **Figure legends**

683 **Figure 1:** Schematic representation of the transitions between the infections-states in
684 herd *x* (*S*: susceptible, *E*: incubating, *I*: infectious, *Q*: chronic, *R*: recovered or naturally
685 resistant). Durations in states *E*, *I* and *Q* are consistent (see Tab. 1 for parameters values
686 and definition), Z_x^i being the number of animals in the i^{th} week of state *Z* (*E*, *I* or *Q*) in
687 herd *x*. The probability of infection for each susceptible animal in herd *x* is
688 $g_x = \left(1 - \exp\left(-\beta_I \sum_{i=1}^{i=d_I} I_x^i\right)\right)$. In each state *Z* in herd *x*, the intake is $\Omega(Z_x)$.

689 **Figure 2:** Global contributions (principal effect plus interactions) of the level of animal
690 movement, of the network degree, of calves recruitment, of shedding period and
691 infectiousness of chronic carriers, and of pathogen virulence to variations in model
692 outputs. See Tab. 4 for outputs' definitions.

693 **Figure 3:** Proportion of realisations with a simulated individual-level reproductive
694 number above one $P(R_0>1)$, according to the pathogen virulence (LVIR: low virulence;
695 HVIR: high virulence), the infectiousness of chronic carriers (β_Q) and the chronic
696 period duration (d_Q). See Tab. 3 for parameters values associated with the scenarios,
697 other parameters being at the reference values.

698 **Figure 4:** Proportion of realisations with a simulated group-level reproductive number
699 above one $P(R^*>1)$ according to the pathogen virulence (LVIR: low virulence; HVIR:
700 high virulence), the infectiousness of chronic carriers (β_Q), the chronic period duration
701 (d_Q), and the movement rate. See Tab. 3 for parameters values associated with the
702 scenarios, other parameters being at the reference values.

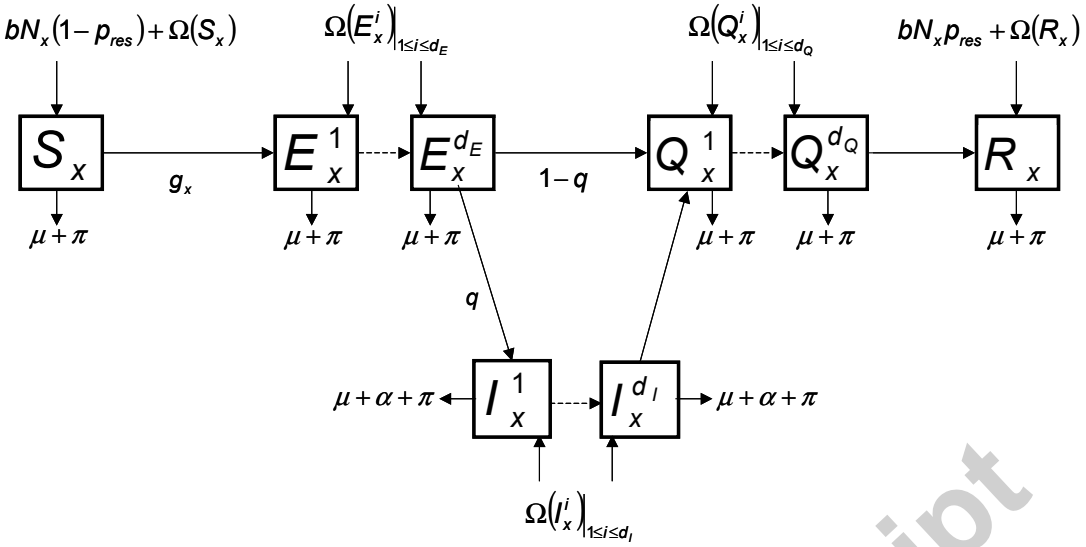
703 **Figure 5:** Average duration (in weeks) of the metapopulation infection (*InfDur*) and the
704 associated standard error, according to the pathogen virulence (LVIR: low virulence;

HVIR: high virulence), the infectiousness of chronic carriers (β_Q), the chronic period duration (d_Q), and the recruitment rate in each herd. See Tab. 3 for parameters values associated with the scenarios, other parameters being at the reference values.

Figure 6: Probability of CBPP endemicity (*P(endemic)* defined as the proportion of realisations with an infection duration over five years) in a bovine metapopulation of sedentary small-sized herds, for a chronic period d_Q = 52 weeks, according to the pathogen virulence (LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers (β_Q), and the recruitment rate in each herd. For a chronic period of d_Q = 26 weeks, *P(endemic)* is nil. See Tab. 3 for parameters values associated with the scenarios, other parameters being at the reference values.

Figure 7: Average epidemic size in infected herds (*EpSiz(H)*) and the associated standard error over a 10-year simulation period, according to the pathogen virulence (LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers (β_Q), the chronic period duration (d_Q), and the recruitment rate in each herd. See Tab. 3 for parameters values associated with the scenarios, other parameters being at the reference values. Note the change of scale, the bold dotted line in (HVIR) being the maximum in (LVIR).

Figure 8: Average epidemic size in infected animals (*EpSiz(I)*) and the associated standard error over a 10-year simulation period, according to the pathogen virulence (LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers (β_Q), the chronic period duration (d_Q), and the recruitment rate in each herd. See Tab. 3 for parameters values associated with these scenarios, other parameters being at the reference values.

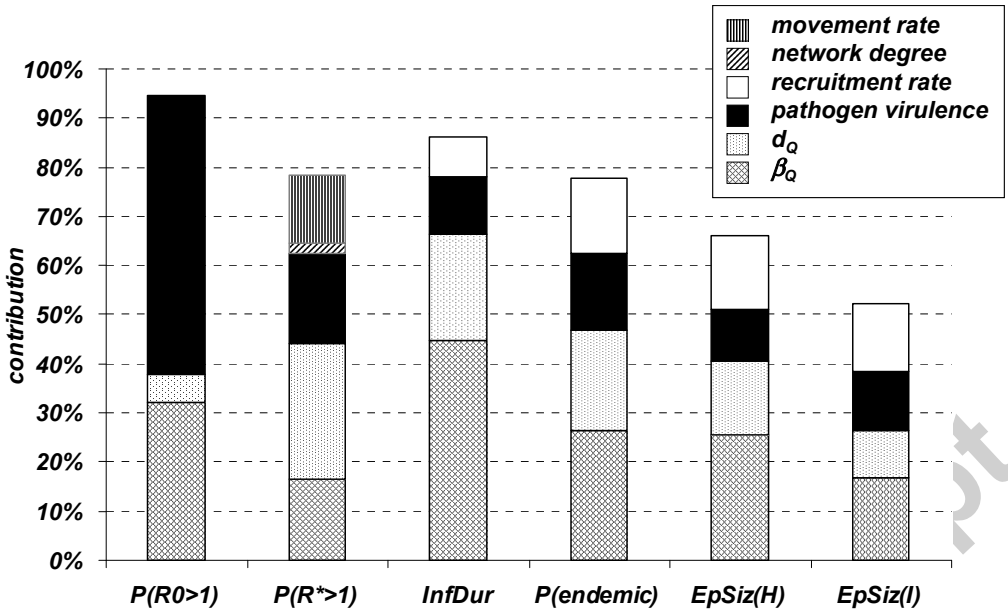


728

729 **Figure 1**

730

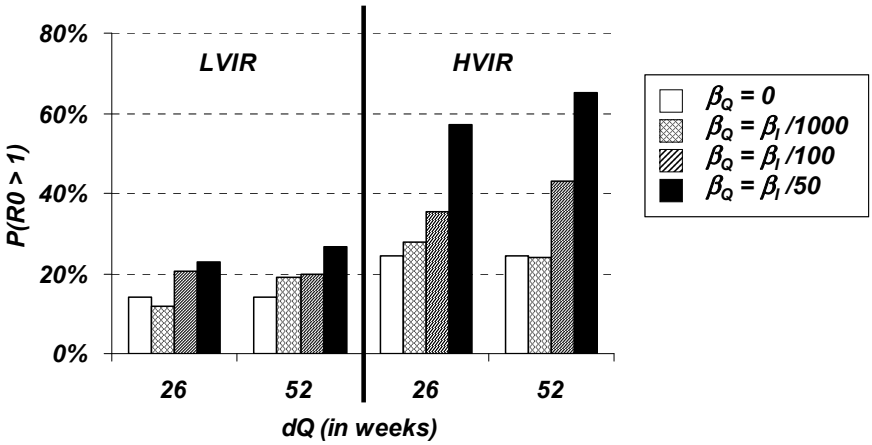
730



731

732 **Figure 2**

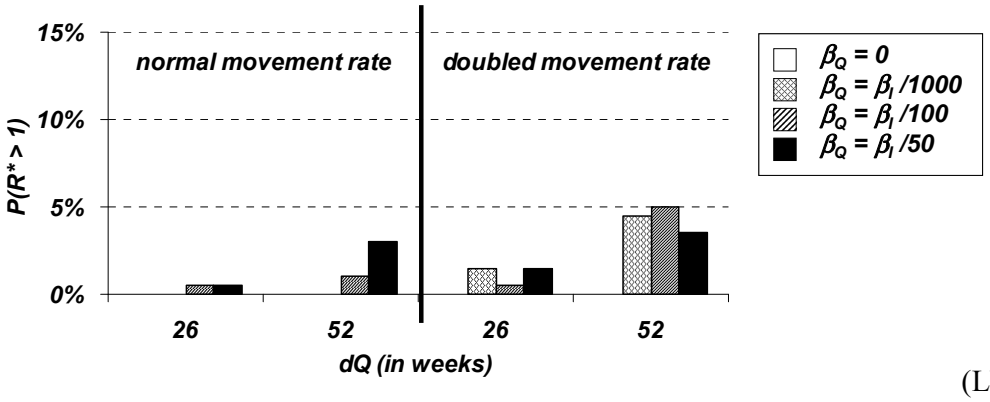
733



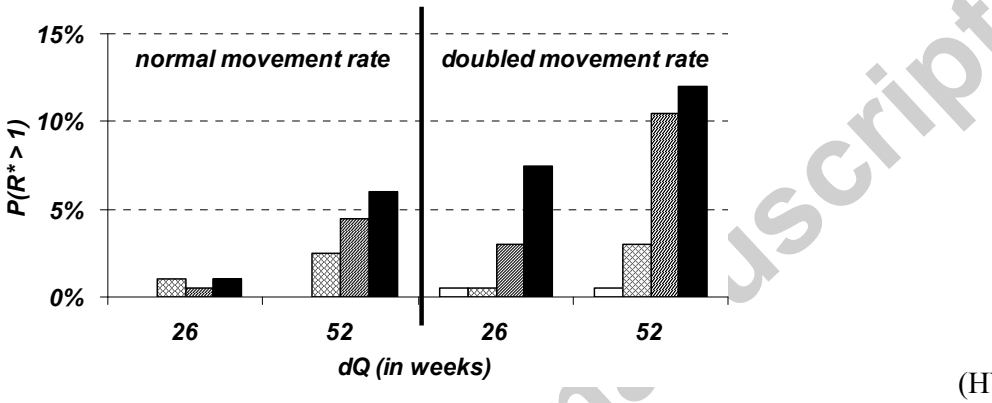
733

734 **Figure 3**

735



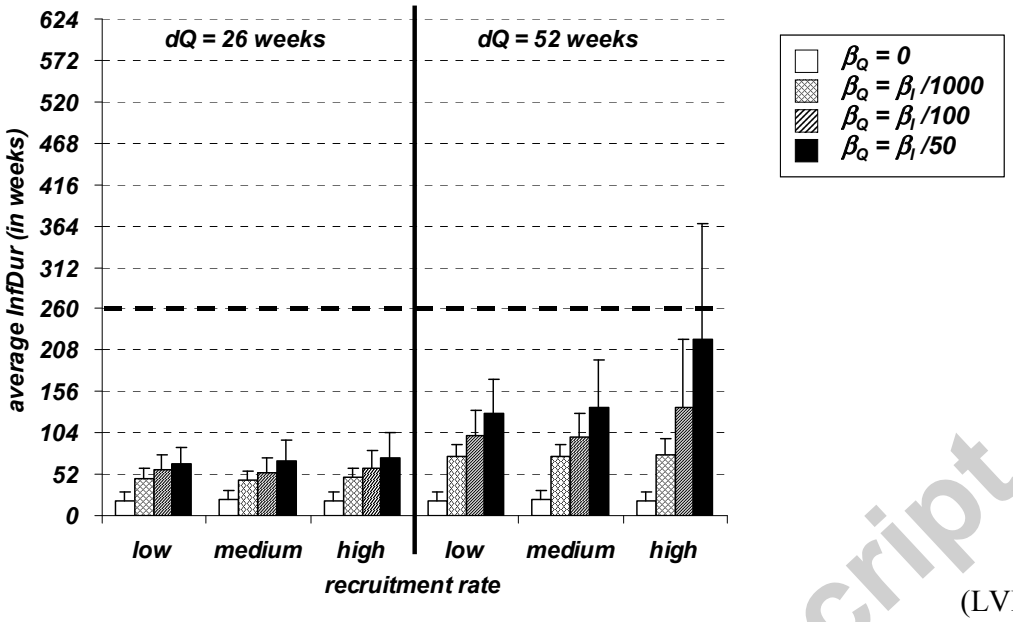
735 (LVIR)



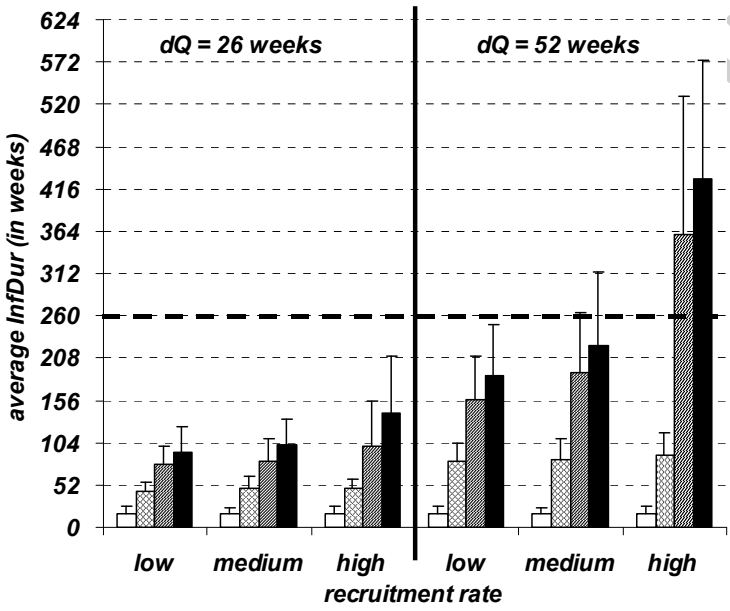
736 (HVIR)

737 **Figure 4**

738



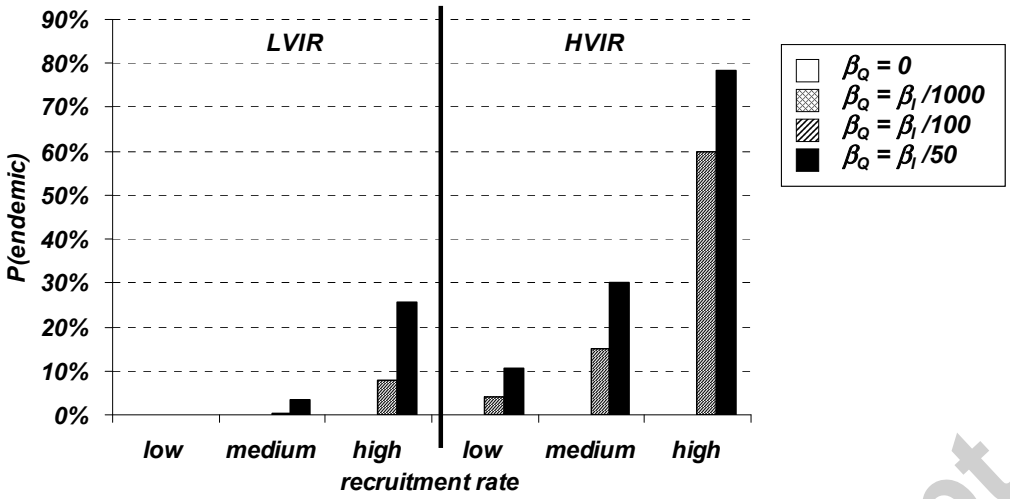
738 (LVIR)



739 (HVIR)

740 **Figure 5**

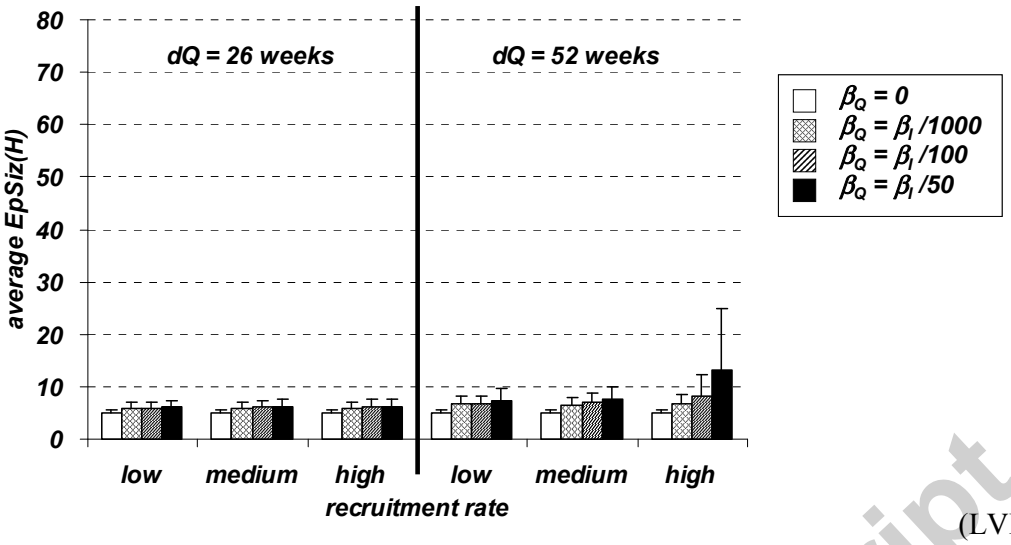
741



741

742 **Figure 6**

743



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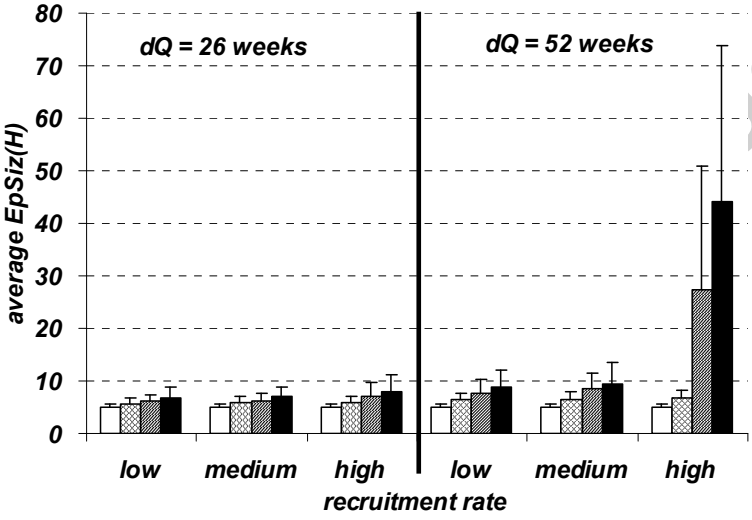
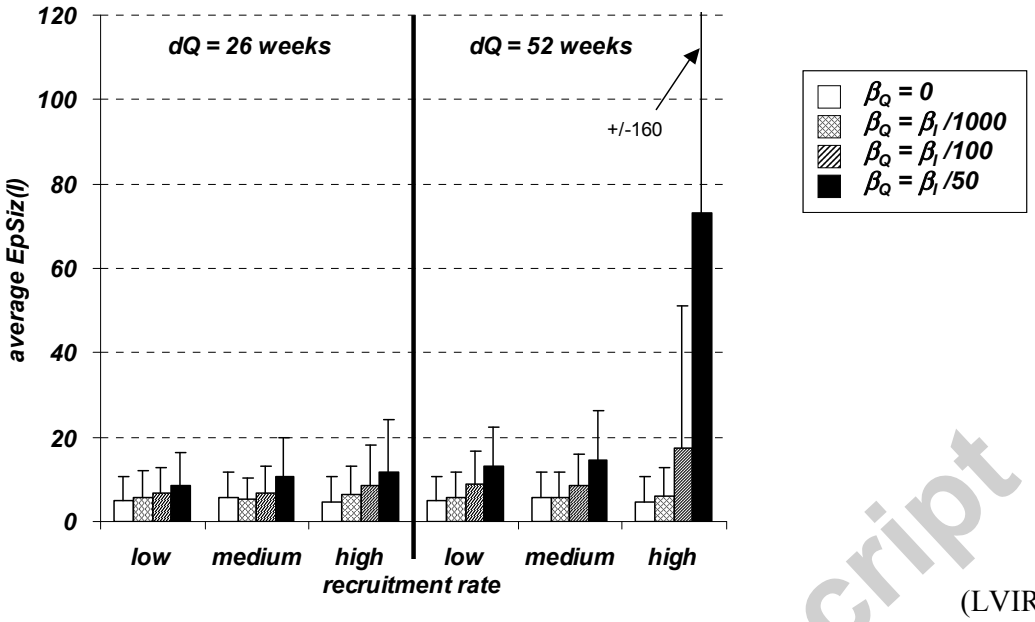


744 (HVIR)

745 **Figure 7**

746



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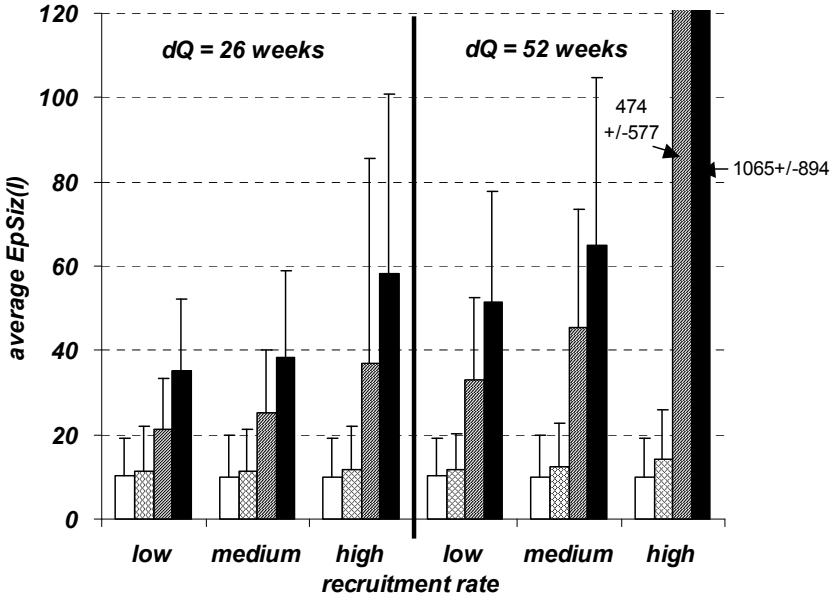

747 (HVIR)

748 **Figure 8**

749